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Prevalence and clinical outcomes of white-coat and masked hypertension: Analysis of a large ambulatory blood pressure database

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The aim of this study was to analyze prevalence and clinical outcomes of the following clinical conditions: normotension (NT; clinic BP < 140/90 mm Hg; 24-hour BP < 130/80 mm Hg), white-coat hypertension (WCHT; clinic BP ≥ 140 and/or ≥90 mm Hg; 24-hour BP < 130/80 mm Hg), masked hypertension (MHT; clinic BP < 140/90 mm Hg; 24-hour BP ≥ 130 and/or ≥80 mm Hg), and sustained hypertension (SHT; clinic BP ≥ 140 and/or ≥90 mm Hg; 24-hour BP ≥ 130 and/or ≥80 mm Hg) in a large cohort of adult untreated individuals. Systematic research throughout the medical database of Regione Lazio (Italy) was performed to estimate incidence of myocardial infarction (MI), stroke, and hospitalizations for HT and heart failure (HF). Among a total study sample of 2209 outpatients, 377 (17.1%) had NT, 351 (15.9%) had WCHT, 149 (6.7%) had MHT, and 1332 had (60.3%) SHT. During an average follow-up of 120.1 ± 73.9 months, WCHT was associated with increased risk of hospitalization for HT (OR 95% CI: 1.927 [1.233-3.013]; *P* = .04) and HF (OR 95% CI: 3.449 [1.321-9.007]; *P* = .011). MHT was associated with an increased risk of MI (OR 95% CI: 5.062 [2.218-11.550]; *P* < .001), hospitalization for HT (OR 95% CI: 2.553 [1.446-4.508]; *P* = .001), and for HF (OR 95% CI: 4.214 [1.449-12.249]; *P* = .008). These effects remained statistically significant event after corrections for confounding factors including age, BMI, gender, smoking, dyslipidaemia, diabetes, and presence of antihypertensive therapies.

1 | INTRODUCTION

Essential hypertension (HT) is a major modifiable risk factor that largely and independently contributes to an increase in cardiovascular (CV) morbidity, mortality, and associated hospitalizations.[1] Over the last few years, a widespread diffusion of automated and semi-automated devices for home and 24-hour ambulatory BP monitoring (ABPM) has been proposed for ameliorating both diagnostic accuracy and therapeutic approaches to uncontrolled HT.[2,3] Indeed, the progressive implementation of these techniques in clinical practice would allow a substantial improvement in patients' awareness of the prognostic relevance of the disease and its potentially life-threatening consequences. They also would ameliorate physicians' ability to tailor antihypertensive therapies to individual characteristics and global CV risk profiles.

As a consequence of the large adoption of validated low-cost and comfortable devices for measuring BP in out-of-hospital settings, some specific patterns of HT have been progressively identified and associated with a substantially higher risk of CV events compared to normotension (NT)—though lower than that observed in SHT or treated, uncontrolled HT. These forms are represented by the so-called white-coat HT (WCHT)[4,5] and masked HT (MHT; aka, reverse white-coat HT),[6,7] which are characterized by isolated and time-limiting BP

rise during the 24-hour period. However, there is conflicting evidence on their prevalence and potential clinical impact on CV morbidity and mortality. This was mostly due to different definitions (ie, BP thresholds), different BP measurements, techniques used, inclusion of both treated and untreated individuals, different sample sizes, and study populations considered.

For these reasons, the primary aim of our analysis was to evaluate the prevalence and the long-term clinical outcomes of NT, WCHT, MHT, and SHT in a large cohort of adult untreated individuals. Secondary aims of the study were to evaluate: (1) prevalence of major CV risk factors and comorbidities, (2) risk of developing predefined CV outcomes, and (3) risk of hospitalization for HT or heart failure (HF) in different BP categories compared to NT.

2 | METHODS

2.1 | Outpatients

For the purposes of the present analysis, we extracted data from our medical database, which included clinical records derived from adult individuals who were consecutively evaluated at the outpatient service of our HT unit at Sant'Andrea Hospital in Rome, Italy. Patients were referred to this center for both diagnostic (untreated individuals) and therapeutic (treated outpatients) purposes. To be included in the study, participants had to present the following inclusion criteria: (1) more than 18 years-old, (2) absence of stable (more than 3 months) pharmacological treatment with any antihypertensive drug, and (3) signature of informed consent for study participation. In addition, the following exclusion criteria were considered: (1) previous or current antihypertensive treatment; (2) secondary hypertension or true resistant hypertension; (3) recent (< 6 months) history of acute CV diseases (including at least one of the following: coronary artery disease, stroke, congestive heart failure, severe valve disease, or peripheral artery disease); and (4) any neurological or psychiatric disease that may at least in part affect the BP assessment or the signature of the informed consent.

The study conformed to the Declaration of Helsinki and its subsequent modifications. The confidentiality of the data of each patient included in the present study was carefully and strictly protected. Informed consent was obtained from all individuals included in the present study, which was approved by the local Ethical Committee.

2.2 | Clinic and 24-hour ambulatory blood pressure measurements

All BP measurements were performed according to recommendations by current HT guidelines;[8] in particular, clinic BP measurements were performed in the HT clinic in the morning (8:00 AM to 10:00 AM) by ESH hypertension specialists. Using an automated oscillometric device (Omron 705 IT, Omron Healthcare Europe BV, Hoofddorp, The Netherlands), sequential BP measurements were performed with the participant in the sitting position, in a quiet room after 10 minutes of rest, and on the same arm. The average of 3 consecutive BP measurements and heart rates were collected at 1-minute intervals and was considered the clinic systolic/diastolic BP levels.[8] All clinic BP measurements were observed.

ABPM was performed by an oscillometric device (Spacelabs 90207, Spacelabs Inc., Redmond, Washington, DC, USA). The device was set in the HT unit after completion of the clinic BP measurements and the monitoring was started at about 10:00 AM. Automatic BP readings were obtained every 15 minutes during the daytime period (from 6:00 AM to 22:00 PM) and every 30 minutes during the night-time period (from 22:00 PM to 6:00 AM) over the 24 hours.[8] Each patient was instructed not to alter her/his usual schedule during the monitoring period, to avoid unusual physical activities, and to keep their arm still during BP measurements. Average values for the 24-hour, daytime, and night-time systolic and diastolic BP levels, and for heart rate were extracted. In addition, standard deviation from average values as well as number of BP measurements above the normal BP thresholds (BP load) was reported for each time period (24-hour, daytime, and night-time) in each participant.

2.3 | Definition of NT and different forms of hypertension

Untreated patients were stratified into 4 BP categories after the assessment of clinic BP and 24-hour ABPM. BP categories were set according to the definitions proposed by current HT guidelines.[8] NT was defined by the presence of both clinic and 24-hour BP levels below the normal thresholds of < 140/90 mm Hg and < 130/80 mm Hg, respectively. WCHT was defined by the presence of abnormal clinic (≥ 140 and/or ≥ 90 mm Hg) and normal 24-hour (< 130/80 mm Hg) BP levels, whereas MHT was defined by normal clinic (< 140/90 mm Hg) and above normal 24-hour (≥ 130 and/or ≥ 80 mm Hg) BP levels. Finally, SHT was defined when both clinic and 24-hour ABPM levels were above the normal thresholds of ≥ 140 and/or ≥ 90 mm Hg and ≥ 130 and/or ≥ 80 mm Hg, respectively. In addition, patients were further stratified on the basis of the presence or the absence of the antihypertensive drug therapies during the follow-up.

2.4 | Definition of cardiovascular risk factors and comorbidities

Development of treated HT was defined by the presence of stable (> 6 months) antihypertensive drug treatment in 2 subsequent visits.[8] The decision to start antihypertensive treatment was made by referring physicians or general practitioners according to individual global CV risk profiles, including clinic and 24-hour BP levels as recommended by current HT guidelines.[8]

Non-fatal myocardial infarction (MI) was defined according to the presence of 2 of the following 3 items: typical symptoms lasting longer than 15 minutes, transient increase in serum concentrations of enzymes indicating cardiac damage (more than twice the upper limit of normal), and electrocardiographic changes typical of myocardial ischemia.[9,10] The diagnosis of MI could also include acute coronary syndrome, recurrent angina, and coronary revascularization.[11]

Non-fatal stroke was defined as a neurological deficit with sudden onset and persistence of symptoms for more than 24 hours, or ultimately leading to death with no apparent causes other than vascular ones.[12] Transient ischaemic attack (TIA) was defined as a neurological event with the signs and symptoms of stroke that go away within a short period of time (typically lasting 2-30 minutes).[13]

Hospitalization due to HT was defined as the presence of a sustained BP raise above 180 and/or 120 mm Hg with or without signs of acute organ damage (HT emergency or urgency, respectively).[8] These events were assessed by emergency room discharge records, according to the definitions proposed by current HT guidelines,[8] and independently by duration and medical treatment administered during hospitalization.

Hospitalization due to HF was defined as the presence of any of the following acute signs or symptoms: effort or rest dyspnoea, pulmonary congestion, lower limb oedema, or venous congestion.[14]

2.5 | Definition of cardiovascular outcomes

Systematic research was performed in the medical database for drug prescriptions provided by a regional health care system (Regione Lazio, Italy) and online. Access to this database is strictly limited to prescribing physicians who have been endorsed by regional health care system. A unique patient code includes demographic data, prescription information, clinical diagnoses, and death. All the diagnoses are coded using the ninth revision of the ICD-9. Compared to baseline observation, the occurrence of MI (ICD-9 410 and 412, stroke or TIA (ICD-9 434.9, 435), HF (ICD-9 428) was determined.

2.6 | Statistical analysis

All data were entered into Microsoft Excel for Windows (Microsoft Office, Microsoft Corp, Redmond, Washington, DC, USA). Baseline characteristics of patients were presented as numbers and percentages for dichotomous variables and mean ± standard deviation (SD) of the mean for continuous variables. Normal distribution of data was assessed using histograms and Kolmogorov-Smirnov test. Differences between continuous variables were assessed using ANOVA test and statistical correction for multiple comparisons among groups (Bonferroni) was applied. Categorical variables were compared among groups by the chi-square test. To evaluate the association among clinical variables and predefined clinical outcomes, odds ratio (OR) and 95% confidence interval (CI) were derived from logistic regression analysis. The following CV outcomes were considered in the present analysis: composite outcome, including MI, stroke, and hospitalization due to HT or HF. Two models for the multivariate analysis were performed. In model 1, the following covariates were included as potential confounding factors: age, BMI, gender (categorical), diabetes (categorical), dyslipidaemia (categorical), and smoking status (categorical). In model 2, we considered the same covariates, but also added the presence or absence of antihypertensive therapy during the follow-up. All tests were two-sided and a *P* value of less than 0.05 was considered statistically significant. All calculations were generated using SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

From an overall sample of 5836 individuals who underwent full BP assessment at our HT unit from January 2007 to December 2015, 3096 (53.0%) were under antihypertensive drug therapies and, thus, were excluded from the analysis. In addition, 128 (2.2%) records were removed for being under 18 years old, 85 (1.4%) records were excluded for being performed during pregnancy or breastfeeding, and 318 (5.4%) records were omitted due to poor quality of the data. In the remaining sample of 2209 adult untreated individuals, which represented 37.8% of the original sample, 377 (17.1%) had NT, 351 (15.9%) WCHT, 149 (6.7%) MHT, and 1332 (60.3%) SHT.

General characteristics of the patients are reported in Table 1. There was a significantly higher prevalence of female subjects in NT (63.9%) and in WCHT (58.7%) compared to those observed in the MHT (40.9%) and in SHT (40.6) groups. There was also a significant trend toward an increase in BMI ($P = .039$) from NT to SHT. Conversely, there was no significant difference among groups with regard to distribution of major CV risk factors and comorbidities, with the exception of dyslipidaemia, which was more prevalent in MHT (7.4%; $P = .013$) compared to other groups. At the same time, lipid lowering drugs and antiplatelet agents were more frequently used in MHT compared to other groups.

3.1 | Blood pressure levels

Average values of clinic and 24-hour BP levels and heart rate in different BP categories are reported in Table 2. As expected, outpatients with WCHT showed higher clinic systolic and diastolic BP levels compared to both MHT (143.5 ± 10.5/92.3 ± 8.1 mm Hg vs 130.3 ± 6.9/83.7 ± 5.2 mm Hg; $P < .001$ for both comparisons) and NT (123.7 ± 9.7/79.2 ± 7.3 mm Hg; $P < .001$ for both comparisons) and lower BP levels compared to SHT (152.0 ± 14.2/99.7 ± 9.7 mm Hg; $P < .001$ for both comparisons). Also, there was a significant trend toward an increase in 24-hour, daytime, and night-time average BP levels from NT to WCHT and MHT to SHT ($P < .001$ for all comparisons).

3.2 | Risk of cardiovascular outcomes

During an average follow-up of 120.1 ± 73.9 months, 713 (32.3%) individuals received antihypertensive drugs, among whom were 91 (24.4%) in NT, 81 (23.1%) in WCHT, 55 (36.9%) in MHT, and 486 (36.5%) in SHT ($P < .001$).

The incidence of the predefined CV outcomes in the overall population sample are reported in Table 3. We observed a significantly higher incidence of the composite outcome and hospitalizations due to HT or HF in those patients with WCHT and MHT compared to those with NT and SHT ($P < .001$ for all comparisons). No significant differences were observed among groups for the incidence of MI and stroke. Higher incidence of predefined CV outcomes was observed in those patients who received antihypertensive drug

TABLE 1 General characteristics of outpatients stratified into 4 BP categories

Parameters	Normotension	White-coat HT	Masked HT	Sustained HT	*P* value
General characteristics					
Individuals (%)	377 (17.1)	351 (15.9)	149 (6.7)	1332 (60.3)	—
Female (%)	241 (63.9)	206 (58.7)	61 (40.9)	541 (40.6)	<.001
Age (y)	52.8 ± 15.9	52.1 ± 13.7	54.8 ± 14.6	52.2 ± 13.1	.149
BMI (kg/m^2)	25.6 ± 4.4	26.1 ± 4.3	26.4 ± 4.4	26.3 ± 4.3**	.039
Risk factors and comorbidities					
Smoking (%)	69 (18.3)	66 (18.8)	28 (18.7)	245 (18.8)	.436
Obesity (%)	51 (13.5)	61 (17.4)	25 (16.8)	209 (15.7)	.527
Dyslipidaemia (%)	24 (6.4)	22 (6.3)	11 (7.4)	47 (3.5)	.013
Diabetes (%)	25 (6.6)	17 (4.8)	11 (7.4)	60 (4.5)	.218
Coronary artery disease (%)	4 (1.1)	1 (0.3)	1 (0.7)	4 (0.3)	.245
Stroke/TIA (%)	2 (0.5)	2 (0.6)	1 (0.7)	8 (0.6)	.998
Drug therapies					
Lipid Lowering drugs	24 (6.4)	22 (6.3)	11 (7.4)	47 (3.5)	.013
Antiplatelet agents	18 (4.8)	22 (6.3)	9 (6.0)	44 (3.3)	.047

BMI, body mass index; IA, transient ischemic attack; THT, hypertension.
**P < .05 vs normotension.

TABLE 2 Clinic and 24-h ambulatory BP levels of outpatients stratified into 4 BP categories

Parameters	Normotension	White-coat HT	Masked HT	Sustained HT	*P* value
Clinic BP measurement					
Systolic BP (mm Hg)	123.7 ± 9.7*,**	143.5 ± 10.5**	130.3 ± 6.9*	152.0 ± 14.2*,**, ***	<.001
Diastolic BP (mm Hg)	79.2 ± 7.3*,**	92.3 ± 8.1**	83.7 ± 5.2*	99.7 ± 9.7*,**, ***	<.001
Heart rate (bpm)	73.6 ± 11.0*	80.0 ± 13.0	77.0 ± 12.0	79.2 ± 11.9***	<.001
24-h BP measurement					
Systolic BP (mm Hg)	116.7 ± 7.5*,**	121.4 ± 5.7**	130.0 ± 7.1*	137.2 ± 12.5*,**, ***	<.001
Diastolic BP (mm Hg)	70.8 ± 5.0*,**	74.2 ± 4.4**	80.7 ± 4.9*	85.9 ± 7.9*,**, ***	<.001
Heart rate (bpm)	73.6 ± 9.1	73.5 ± 9.4	74.2 ± 8.5	74.4 ± 8.9***	.006
Daytime BP measurement					
Systolic BP (mm Hg)	119.8 ± 7.8*,**	125.9 ± 6.2**	133.2 ± 6.7*	141.7 ± 10.7*,**, ***	<.001
Diastolic BP (mm Hg)	74.1 ± 5.7*,**	78.4 ± 5.1**	83.7 ± 5.8*	90.0 ± 8.3*,**, ***	<.001
Heart rate (bpm)	75.5 ± 9.8	77.0 ± 10.1	77.3 ± 9.3	77.5 ± 9.6***	.006
Night-time BP measurement					
Systolic BP (mm Hg)	109.4 ± 9.1**	111.2 ± 7.4**	122.2 ± 10.9*	126.0 ± 12.6*,**, ***	<.001
Diastolic BP (mm Hg)	63.3 ± 5.8*,**	64.8 ± 5.1**	73.0 ± 6.4*	75.6 ± 8.6*,**, ***	<.001
Heart rate (bpm)	65.0 ± 8.7	65.5 ± 9.6	67.2 ± 9.1	66.9 ± 9.0***	.001

BP, blood pressure; HT, hypertension.
*P < .05 vs white-coat HT, **P < .05 vs masked HT, ***P < .05 vs normotension.

therapies during the follow-up (Table 4a,), particularly in those with MHT compared to other groups (P < .001 for all comparisons). The incidence of the same CV events in patients who remained untreated during the follow-up was generally low (Table 4b), with a significantly higher incidence of stroke (P = .011) and hospitalization due to HT (P < .001) and HF (P = .003) in WCHT patients compared to other groups.

Univariate and multivariate analyses for the risk of developing the predefined CV outcomes are shown in Table 5. Taking NT as reference group, WCHT was associated with a reduced risk (unadjusted OR 95% CI: 0.582 [0.446-0.759]; adjusted OR 95% CI: 0.593 [0.450-0.780]; P < .001), whereas SHT was associated with higher risk (unadjusted OR 95% CI: 1.645 [1.363-1.985]; adjusted OR 95% CI: 1.696 [1.390-2.068]; P < .001) of receiving antihypertensive drug therapy during

TABLE 3 Incidence of the predefined cardiovascular outcomes during the follow-up in the overall population sample, stratified into 4 BP categories

Parameters	NT	White-coat HT	Masked HT	Sustained HT	*P* Value
Composite outcome (MI + stroke + any hospitalization)	32 (8.5)	48 (13.7)	24 (16.1)	101 (7.6)	<.001
Myocardial infarction	13 (3.4)	9 (2.6)	11 (7.4)	41 (3.1)	.037
Stroke	7 (1.9)	7 (2.0)	4 (2.7)	12 (0.9)	.122
Hospitalization for any cause	22 (5.8)	35 (10.0)	18 (12.1)	54 (4.1)	<.001
Hospitalization for HT	22 (5.8)	31 (8.8)	17 (11.4)	5 (3.8)	<.001
Hospitalization for HF	1 (0.3)	7 (2.0)	5 (3.4)	6 (0.5)	<.001

HF, heart failure; HT, hypertension; MI, myocardial infarction.

TABLE 4 Incidence of the predefined cardiovascular outcomes during the follow-up in those patients who received antihypertensive drug therapies (panel a) and in those who remained untreated (panel b) during the follow-up, according to 4 BP categories

Parameters	NT	White-coat HT	Masked HT	Sustained HT	*P* value
(a)					
Composite outcome (MI + Stroke + Any Hospitalization)	32 (8.5)	24 (26.9)	23 (41.8)	72 (14.8)	<.001
Myocardial infarction	13 (14.3)	7 (8.6)	11 (2.0)	28 (5.8)	<.001
Stroke	7 (7.7)	0 (0.0)	3 (5.5)	6 (1.2)	<.001
Hospitalization for any cause	22 (24.2)	20 (24.7)	18 (32.7)	43 (8.8)	<.001
Hospitalization for HT	22 (24.2)	17 (21.0)	17 (30.9)	39 (8.0)	<.001
Hospitalization for HF	1 (1.1)	4 (4.9)	5 (9.1)	6 (1.2)	.001
(b)					
Composite outcome (MI + Stroke + Any Hospitalization)	0 (0.0)	24 (8.9)	1 (1.1)	29 (3.4)	<.001
Myocardial infarction	0 (0.0)	2 (0.7)	0 (0.0)	13 (1.5)	.091
Stroke	0 (0.0)	7 (2.6)	1 (1.1)	6 (0.7)	.011
Hospitalization for any cause	0 (0.0)	15 (5.6)	0 (0.0)	11 (1.3)	<.001
Hospitalization for HT	0 (0.0)	14 (5.2)	0 (0.0)	11 (1.3)	<.001
Hospitalization for HF	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	.003

HF, heart failure; HT, hypertension; MI, myocardial infarction.

the follow-up, even after adjusting for age, gender, BMI, dyslipidaemia, and diabetes.

Both WCHT and MHT showed an independent predictive role in the risk of having the composite outcome of MI, stroke, and hospitalization, even after adjusting for age, gender, BMI, smoking, dyslipidaemia, and diabetes (model 1), as well as for antihypertensive therapy (model 2). On the other hand, SHT was associated with a reduced risk of the composite outcome in both models of the multivariate analysis.

MHT was the only significant predictor of an increased risk of having MI at both univariate and multivariate analyses, whereas no significant association was found for WCHT with regard to MI outcome. Conversely, SHT was associated with a reduced risk of developing stroke or TIA at univariate analysis, although this effect was not supported at multivariate analysis.

Finally, WCHT and MHT showed a significantly increased risk of hospitalization due to HT and HF in univariate and in both models of multivariate analyses, whereas SHT was associated with a reduced risk of hospitalizations.

4 | DISCUSSION

High clinic (or office) BP levels are strongly and independently related to increased risk of CV outcomes. In the recent years, however, several studies suggest that temporal and time-limiting increases in BP levels, measured in out-of-office settings, and mostly during the night-time, can be related to a substantially higher risk of developing HT-related complications than those predicted on the basis of clinic BP assessment.[15-27] These observations suggest a potential role of clinical conditions, such as WCHT and MHT, in the pathophysiological processes involved in the development and progression of structural and functional abnormalities that can be found at cardiac and vessel levels in asymptomatic hypertensive patients at different

TABLE 5 Univariate and multivariate analyzes of the risk of developing treated hypertension, myocardial infarction, stroke, hospitalization for hypertension and hospitalization for heart failure during the follow-up according to BP strata. Those parameters showing significant predictive value for the predefined outcomes at univariate analysis, were adjusted for age, gender, body mass index, smoking, dyslipidaemia, and diabetes at multivariate analysis

	Unadjusted		Adjusted—Model 1		Adjusted—Model 2	
Parameters	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Composite outcome (MI + Stroke + any hospitalization)						
White-coat HT	1.716 (1.215-2.425)	.002	1.791 (1.244-2.578)	.002	2.360 (1.596-3.489)	<.001
Masked HT	1.993 (1.255-3.166)	.003	1.757 (1.066-2.893)	.027	1.616 (0.948-2.753)	.078
Sustained HT	0.610 (0.457-0.814)	.001	0.628 (0.461-0.854)	.003	0.503 (0.363-0.698)	<.001
Outcome myocardial infarction						
White-coat HT	0.753 (0.263-2.161))	.598	—	—	—	—
Masked HT	7.739 (3.657-16.378)	<.001	5.062 (2.218-11.550)	<.001	4.118 (1.692-10.019)	.002
Sustained HT	0.294 (0.039-0.624)	.001	0.327 (0.150-0.714)	.005	0.279 (0.123-0.636)	.002
Outcome stroke						
White-coat HT	1.206 (0.454-3.206)	.707	—	—	—	—
Masked HT	2.443 (0.834-7.159)	.103	—	—	—	—
Sustained HT	0.448 (0.207-0.970)	.042	0.524 (0.237-1.161)	.111	0.520 (0.234-1.155)	.108
Outcome hospitalization for HT						
White-coat HT	1.926 (1.258-2.947)	.003	1.927 (1.233-3.013)	.04	2.608 (1.619-4.202)	<.001
Masked HT	2.447 (1.422-4.210)	.001	2.553 (1.446-4.508)	.001	2.449 (1.335-4.491)	.004
Sustained HT	0.450 (0.310-0.653)	<.001	0.450 (0.302-0.671)	<.001	0.325 (0.213-0.496)	<.001
Outcome hospitalization for HF						
White-coat HT	3.130 (1.224-8.007)	.017	3.449 (1.321-9.007)	.011	4.334 (1.605-11.699)	.004
Masked HT	5.074 (1.803-14.285)	.002	4.214 (1.449-12.249)	.008	3.545 (1.160-10.837)	.026
Sustained HT	0.301 (0.114-0.794)	.015	0.316 (0.117-0.852)	.023	0.268 (0.096-0.752)	.012

CI, confidence intervals; HF, heart failure; HT, hypertension; OR, odds ratio.

CV risk profile, thus leading to higher risk of experiencing major CV events.[15-27] Our analysis is consistent with this hypothesis and with the main findings of previous clinical studies, performed in the setting of Italian,[28,29] Spanish,[30] Afro-American,[31] and Japanese[32] outpatients. These analyses, in fact, reported a higher risk of developing CV accidents in patients with WCHT or MHT compared to NT.[28-32] As an example, in a clinical study performed in Italy on 2051 adult individuals who underwent systematic assessment of home, clinic, and ambulatory BP levels, WCHT and MHT was diagnosed in about 17% and 8% of the subjects, respectively, and associated with higher risk of CV and all-cause mortality compared to NT, although lower risk than those observed in SHT.[28,29] Similarly, in the study by Ohkubo et al,[32] WCHT and MHT were associated with higher CV mortality, whereas only MHT was associated with higher risk of stroke compared to NT. It should be noted, however, that these studies often included treated hypertensive patients among those classified as WCHT or MHT and the independent role of MHT and WCHT on CV morbidity and all-cause mortality was not consistently demonstrated.[28-32] On the other hand, in the International Database of Home Blood Pressure in Relation to Cardiovascular Outcome (IDHOCO), WCHT, assessed by home BP measurements, resulted a CV risk factor only in untreated outpatients. This was probably because the latter received effective treatment on the basis of their elevated clinic BP levels. In contrast, MHT was associated with increased CV risk in both untreated and treated patients, who are probably undertreated because of their normal clinic BP levels.[33,34] In order to avoid the potential confounding impact of antihypertensive treatment on the diagnosis of WCHT and MHT, all treated hypertensive patients have been systematically excluded by our analysis, thus leading to a large and homogenous sample of adult untreated individuals at low-to-moderate CV risk profiles in whom the prognostic role of these conditions can be tested independently by the presence or absence of antihypertensive treatment at baseline.

Our analysis primarily demonstrated an independent role of WCHT and MHT in predicting hospitalizations for HT or HF and confirmed the independent predictive role of MHT on the risk of experiencing MI during the follow-up period. Indeed, in our study the lowest incidence of hospitalization was observed in the SHT group compared to other groups. This was probably due to the fact that a higher proportion of patients included in this group received pharmacological therapies during the follow-up compared to other ones. In fact, when we stratified the BP subgroups on the basis of the assumption (or not) of antihypertensive drugs during the follow-up, the incidence of predefined CV outcomes was lower in the SHT when compared to those observed

in other groups, including MHT, WCHT, and NT (also observed in previous studies).[33,34] This seems to suggest that early initiation of antihypertensive therapy in SHT patients may have at least in part reduced the risk of CV outcomes compared to those observed in NT individuals who received antihypertensive drugs during the follow-up. Although we were not able to analyze the BP control rates achieved in different study groups, it can be argued that the use of BP lowering therapies may have had a favorable impact on the observed risk of having CV events or hospitalizations during the follow-up period. This may also imply that a more systematic assessment of WCHT and MHT throughout 24-hour ABPM would facilitate the early identification of otherwise healthy individuals with normal or above-normal clinic BP levels who are at high-risk of developing major CV events, thus allowing the implementation of pharmacological and non-pharmacological interventions aimed at reducing this risk. The relatively limited number of CV events observed in our analysis, however, does not allow any definite consideration on this finding.

Indeed, our analysis demonstrated that BP levels independently (based on how they have been measured) showed a trend toward increase from NT towards SHT, thus suggesting that both WCHT and MHT should be considered potentially harmful conditions. In fact, despite the relatively low prevalence (WCHT plus MHT represents about one-third of the overall study sample), both of these conditions heavily impact CV prognosis in our sample. In addition, it has been previously demonstrated that adult individuals with high-normal BP levels or pre-HT may have higher CV risk than those with NT.[35,36]

As a final consideration, the rigorous and proper definition of WCHT and MHT, based on both clinic and 24-hour BP levels, as recommended by current HT guidelines,[8] and the relatively young age of our sample may at least in part justify the absence of correlation between these conditions and risk of stroke compared to those reported by previous studies,[24,37] even though both WCHT and MHT have been associated to high-risk of hospitalizations. This apparent discrepancy can be at least in part explained by the fact that in some cases definitions of these clinical conditions have been based on either home or daytime BP rather than 24-hour BP levels. In addition, BP thresholds adopted in previous studies may largely vary according to both authors' decisions and references' populations, as well as depending on the BP criteria proposed by previous sets of HT guidelines.

4.1 | Potential limitations

The present study has some potential limitations that should be acknowledged. First of all, data were retrospectively extracted from a single-center medical database for the purposes of the present analysis, and not prospectively collected during clinical consultations. For this reason, our findings can only provide associations among baseline parameters, namely BP levels and categories, and subsequent clinical consequences, but they cannot provide explanations for the observed risk of outcomes. At the same time, the occurrence of the predefined clinical events was derived from data extrapolated from the regional database for drug prescriptions and not assessed by an independent event committee. In this latter regard, however, it should be also noted that all the diagnoses were reviewed and certified by different and independent health professional figures, including hospital discharge reports, referring physicians, and local health care providers, before being included in this database. Since all available data were extracted from the regional database in a single occasion, we cannot discriminate when the predefined cardiovascular outcomes occurred, but only if they occurred (ie, presence or absence of the outcomes at the time of data extraction). In addition, we did not consider fatal CV and non-CV events that occurred during the follow-up period. MHT patients were classified according to the presence of normal clinic BP values and above normal values of either systolic or diastolic 24-hour BP levels, as also applied in previous surveys.[38] This may imply that these patients might have normal 24-hour systolic BP in the presence of above normal 24-hour diastolic BP, and vice-versa. Average BMI values for all groups was in line with the median values of the Italian general population,[39,40] and appeared to be lower than that reported in studies performed in the US.[41,42] However, data on metabolic and renal parameters (including estimated glomerular filtration rate), as well as markers of organ damage and other non-CV comorbidities, were not addressed, and this aspect may at least in part explain the relatively low prevalence of diabetes and other metabolic risk factors observed in our population sample. Finally, despite high smoking rates of about 19% (almost 1 in 5), we have no data on the average pack/data rate for smokers included in the study sample.

5 | CONCLUSIONS

Our findings confirmed that, despite their relatively low prevalence, both WCHT and MHT were associated with an increased risk of developing MI and hospitalizations for HT and HF in a relatively small population sample of adult untreated individuals at a low-to-moderate CV risk profile. Further studies are needed to better clarify the potential clinical implications of other diagnostic parameters and of antihypertensive therapies in these BP categories compared to NT and SHT.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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